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The Determination of Narcotine and Meconic Acid in Opium. Second Method. (A Report from the Government Laboratory, London, England)

By J.R. Nicholls and E.G. Kellett

In continuation of the international programme of scientific research undertaken pursuant to resolution 246 F (IX), and adopted by the Economic and Social Council on 6 July 1949, the Secretary-General is now publishing three articles, Nos. 5, 5, and 7 in this series, on the determination of narcotine and meconic acid in opium. These three articles present three different methods successively worked out at the Government Laboratory, London, England. While the third method to a great extent supersedes the first two, the Secretary-General considers that the first two methods include features which may be suggestive and helpful to the chemists working on opium, and that they are so different from the third method as to warrant separate publication. The present paper gives the second of these methods.

The Determination of Narcotine and Meconic Acid in Opium

Second Method

By J.R. Nicholls and E.G. Kellett

A report from the Government Laboratory, England

I. SYNOPSIS

1. The opium is extracted with cold 2 per cent acetic acid. Narcotine and barium meconate, with other constituents, are precipitated from the extract by making slightly alkaline in the presence of barium chloride. The narcotine is washed out of the precipitate with acetone, purified by precipitation from the acetone solution with dilute sodium hydroxide, and redissolved in acetone. The acetone solution is finally filtered, evaporated and dried at 100°C.

2. The acetone-washed precipitate from the opium extract is treated with dilute sulphuric acid to convert barium meconate into meconic acid, which is then brought into solution by adding sodium bicarbonate. This solution, after filtration, is made more strongly alkaline so as to form the sparingly soluble trisodium meconate which is precipitated by saturating with sodium chloride. The trisodium salt, after filtering and washing with aqueous alcohol saturated with sodium chloride, is determined by titration as a mild alkali to brom-phenol blue.

II. DISCUSSION

3. For the extraction of narcotine and meconic acid from opium, 2 per cent acetic acid appears the most suitable solvent of those which have been tried. It causes no radical decomposition, and dissolves only minimal amount of resins and neutral substances; it is sufficiently acid to bring the basic alkaloids, including narcotine, into solution, but not so acid as to repress the solubility of meconic acid as mineral acids do.

4. Narcotine, being a feebler base than the other preponderant alkaloids in the extract, is accordingly precipitated at a lower pH. The point of neutrality to cresol red (pH about 8) has been found suitable in practice. Adjustment to this pH in the presence of alcohol (about 40 per cent) will indeed precipitate the narcotine from an opium extract in sufficient purity to appear as well-formed and characteristic crystals. The presence of alcohol, however, involves a positive, though small, residual solubility of narcotine, and is also an inconvenience in causing meconates to precipitate in a gelatinous form which is not easily washed.

/The narcotine

The narcotine is therefore precipitated in slightly cruder form from aqueous solution only, and is easily purified by making use of its ready solubility in acetone and insolubility in dilute sodium hydroxide solution.

5. The opium extract is liable to contain some calcium salts, which at pH8 would bring down some meconic acid as calcium meconate. Barium chloride is therefore added, to ensure the precipitation of substantially the whole of the meconic acid at this stage. No conditions have been found in which the mother-liquor does not give a distinct meconic acid reaction with ferric chloride. Precipitation as the lead salt appears to be more complete; the difference between the two however has in quantitative terms been found to be very small, the ferric chloride reaction being a highly sensitive one; and precipitation with barium gives a product so much less slimy and more workable that this method is for practical purposes preferred.

6. Trisodium meconate, in which the hydrogen of a hydroxyl group as well as two carboxyl groups is replaced by sodium, is a yellow salt of characteristic appearance, sparingly soluble in water on the alkaline side of neutrality. Its solubility may be further repressed by the presence of alcohol, and if it is desired to prepare and dry the pure salt, this is often a practicable procedure. In some cases, however, the presence of alcohol causes precipitation of trisodium meconate from an opium extract in a gelatinous form which is very difficult to wash free from the mother-liquor. For purposes of determination without isolation, therefore, it is preferred to repress the solubility by increased concentration of sodium ion (saturation with sodium chloride); as the volume of solution, following on concentration of the meconic acid in the form of the barium salt, can be kept quite small, the residual solubility effect is in fact neglibible. The salt thus precipitated can be easily washed with alcoholic brine until contaminated only with sodium chloride, and then determined by titration to brom-phenol blue (conversion of trisodium to disodium salt).

III. EXPERIMENTAL PROCEDURE

7. Extraction. 5 g. opium are triturated with 2 ml acetone, which facilitates the breaking down of sticky lumps and, drying off during the process, leaves the opium as a friable powder readily accessible to the action of the solvent.

8. The powdered material is well shaken with 40 ml 2 per cent acetic acid, and left with occasional shaking for some hours. 1 g.of a siliceous filter-aid is shak

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shaken in, and the mixture filtered with suction. The solid residue is returned to the extraction vessel; with its admixture of filter-aid, it should detach cleanly from the funnel and paper. The paper is rinsed with 20 ml of 2 per cent acetic acid, which is then used for a further extraction of the solid residue. This procedure is followed, without further additions of filter-aid, for two or three further extractions with 20 ml portions of 2 per cent acid. The last filtrate should show not more than a slight meconate reaction with ferric chloride.

9. A convenient way of applying this reaction as a test in the presence of acetates etc. is to make up a 10 per cent solution of sodium acetate, add ferric chloride until a strong colour is developed, then add a measured amount of conc. hydrochloric acid from a burette until the colour is discharged and the solution remains only a pale greenish yellow. Then add further hydrochloric acid equal to one-tenth of the volume already added. Treatment of a portion of this reagent with one-tenth of its volume of a solution containing acetate will only restore the proportions at which no acetate colour is developed, and any marked red or purple colour may be regarded as due to meconate. The reaction is so sensitive that a slight colour is of no practical quantitative significance, and to continue extraction of the opium until the reaction is entirely negative would be no more than an unprofitable dilution of the extract.

10. Separation of narcotine. To the combined extracts, 2 g. barium chloride, dissolved in a little hot water, is added. 10 per cent sodium hydroxide solution is then gradually added until a drop of the liquid reacts definitely pink to cresol red. The extract is sufficiently a buffer in its properties to make the colour-change quite gradual and easily controlled. The mixture is well-stirred and allowed to stand, preferably overnight.

11. 1 g. of filter-aid is stirred in, and the solid filtered with suction, washed with water until the washings are colourless, and pressed and sucked as dry as possible. The solid is extracted by several times breaking up the cake with a little acetone, and sucking through into a clean receiver. Care should be taken to counter creeping of narcotine up the side of the funnel. A total volume of more than about 25 ml acetone is unnecessary and undesirable.

12. The acetone solution is precipitated by the addition of ten times its volume of water, and allowed to stand, with occasional stirring, until the supernatant liquid is clear. 0.5 g. of sodium hydroxide, dissolved in water, is then stirred in; the solid narcotine is filtered off, washed with water until the washings are

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neutral, then washed through with acetone into an open vessel in which the acetone can be evaporated and the residue dried and weighed. The solid narcotine thus finally obtained should be colourless and well crystallized, with a melting-point not below 172°C. In a doubtful case, it may be purified by taking up in a little acetone and repeating the precipitation. With pure narcotine, the loss due to such treatment is less than 0.01 gm. provided that precipitation with water is effected before the addition of alkali, though direct addition of caustic alkali to the acetone solution may cause loss of narcotine by opening of the lactone ring.

13. Separation of trisodium meconate: The original precipitate from the opium extract, after washing out the narcotine with acetone, is washed with a little alcohol and alcohol-chloroform to remove possible small amounts of other alkaloids. It is then removed from the filter and broken up with 10 ml N. sulphuric acid. After standing for an hour, 1 g. sodium bicarbonate is stirred in, and the mixture filtered. The solid residue is washed with two portions each of 7-8 ml water. To the filtrate and washings, 2 ml N. sodium hydroxide are added, and solid sodium chloride is gradually stirred in until a little remains undissolved. After standing for a few hours, the precipitated trisodium meconate is filtered off and washed with 50 per cent aqueous alcohol, saturated with sodium chloride, until the washings are colourless and neutral to phenolphthalein. The residue should be a granular powder of a clear lemon-yellow, and when dissolved in 20 ml N/10 sulphuric acid should show little or no brown or red colour; it may then be back-titrated to brom-phenol blue with N/10 sodium hydroxide. 1 ml N/10 acid is equivalent to 0.020 g. meconic acid. If the solution before titration is noticeably discoloured, re-precipitation by making alkaline and again salting out is an effective means of purification, and involves no significant loss.